Cannabis (Medical Marijuana) Treatment for Motor and Non–Motor Symptoms of Parkinson Disease: An Open-Label Observational Study

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Objective: The use of cannabis as a therapeutic agent for various medical conditions has been well documented. However, clinical trials in patients with Parkinson disease (PD) have yielded conflicting results. The aim of the present open-label observational study was to assess the clinical effect of cannabis on motor and non–motor symptoms of PD.

Methods: Twenty-two patients with PD attending the motor disorder clinic of a tertiary medical center in 2011 to 2012 were evaluated at baseline and 30 minutes after smoking cannabis using the following battery: Unified Parkinson Disease Rating Scale, visual analog scale, present pain intensity scale, Short-Form McGill Pain Questionnaire, as well as Medical Cannabis Survey National Drug and Alcohol Research Center Questionnaire.

Results: Mean (SD) total score on the motor Unified Parkinson Disease Rating Scale score improved significantly from 33.1 (13.8) at baseline to 23.2 (10.5) after cannabis consumption ($t = 5.9$; $P < 0.001$). Analysis of specific motor symptoms revealed significant improvement after treatment in tremor ($P < 0.001$), rigidity ($P = 0.004$), and bradykinesia ($P < 0.001$).

Conclusions: There was also significant improvement of sleep and pain scores. No significant adverse effects of the drug were observed. The study suggests that cannabis might have a place in the therapeutic armamentarium of PD. Larger, controlled studies are needed to verify the results.

Key Words: cannabis, Δ9-THC, Parkinson disease, pain

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Cannabis, also known as marijuana (from the Mexican Spanish, marihuana), is prepared from the *Cannabis sativa* plant. Its principal psychoactive constituent, Δ9-tetrahydrocannabinol (THC), was isolated in 1964 by Gaoni and Mechoulam.[1] Other cannabinoids among the 400 compounds contained in the plant are cannabidiol, cannabinol, and tetrahydrocannabivarin. The potential use of cannabis in the pharmacotherapy of pain and various diseases (medical marijuana), including cancer, glaucoma, and multiple sclerosis, has been well documented.[2–6]

In Israel, marijuana was legalized for medical use in various conditions in the 1990s. The authorization of cannabis treatment for Parkinson disease (PD) was prompted by Israeli media reports of dramatic improvement of tremor in 1 patient and amelioration of symptoms in others. However, the findings have not been corroborated in controlled studies. Overall, there are currently very few double-blind, controlled studies on the effect of cannabis on motor deficits in PD, and the results are often conflicting. Most of the existing literature focuses mainly on the effect of cannabinoid agonists on dyskinesias.

The aim of the present study was to evaluate the efficacy of cannabis treatment in alleviating the motor and non–motor symptoms of PD in a clinical setting.

PATIENTS AND METHODS

Twenty-eight patients with PD attending the movement disorder clinic at Rabin Medical Center, a tertiary, university-affiliated hospital, had received permission to smoke cannabis from the Israel Ministry of Health as an add-on therapy because their anti-Parkinson medications had proved insufficient or to combat severe PD-related pain and tremor from June 2011 to April 2012. Patients were eligible for the study if they were treated with cannabis on a daily basis for at least 2 months and tolerated the drug with no major adverse effects. Six patients could not tolerate the drug and discontinued treatment after a short period because of severe adverse effects (inability to smoke, vomiting, dizziness, and psychosis). Twenty-two patients were included in the study. Seven patients had response fluctuations. The study protocol was approved by the local research ethics committee, and all patients gave written informed consent.

On the day of the study, eligible patients were instructed to arrive at the clinic without taking their regular medications so that their baseline motor status could be assessed. Patients with motor fluctuations were to be examined during the "off" period: Those who could not delay their morning dose were asked to wait at the clinic for onset of the off period before smoking cannabis; if they were unable to wait, they were examined during the "on" period.

At baseline, disease staging was performed using the Hoehn and Yahr rating scale. Additional data on motor symptoms and signs were collected with the motor part of the Unified PD Rating Scale (UPDRS); those on non–motor symptoms, with a visual analog scale and present pain intensity scale, the Short-Form McGill Pain Questionnaire, as well as the Medical Cannabis Survey National Drug and Alcohol Research Center Questionnaire. The latter questionnaire was adopted from a previous survey conducted in Australia on mode of use, subjective efficacy, and adverse effects of cannabis.[7] Thereafter, the patients were asked to smoke their regular dose of cannabis (amount inhaled, 0.5 g). Thirty minutes later, the motor and non–motor battery was repeated.

The effect of cannabis consumption on motor symptoms was evaluated by 2 raters (I.L. and R.D.) to avoid diversions and assure the credibility of the results. Interrater variability was analyzed with the Pearson correlation. Paired sample *t* test was used to compare values of the various parameters before

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TABLE 1. Clinical Characteristics of Patients With PD Treated With Cannabis

Patient No.	Age, y/Sex	Disease Duration, y	Response Fluctuations	Past Pain	Current Medications
1	62/M	3	Yes	Yes	Levodopa
2	63/M	5	No	Yes	Levodopa, amantadine
3	70/F	11	Yes	No	Rasagiline, ach, selegiline
4	57/M	8	No	Yes	Levodopa, amantadine
5	54/M	9	Yes	Yes	Levodopa, rasagiline
6	77/M	6	No	No	Levodopa, ach, selegiline
7	58/M	18	No	Yes	Levodopa
8	64/F	7	Yes	Yes	Levodopa, pramipexole, rasagiline
9	60/F	14	No	No	Levodopa
10	42/M	3	No	Yes	Stalevo, amantadine, pramipexole, selegiline, ach
11	73/F	3	No	No	Levodopa, ach, selegiline
12	74/M	5	No	Yes	Levodopa, pramipexole, amantadine
13	52/F	5	No	Yes	Levodopa, rasagiline
14	73/M	11	Yes	Yes	Levodopa, ropinirole, amantadine
15	65/F	16	No	No	Levodopa, rasagiline, ach, selegiline
16	63/F	2	No	Yes	Levodopa, rasagiline
17	80/M	4	No	No	Rasagiline, ach, selegiline
18	70/M	2	No	Yes	Levodopa, selegiline
19	71/M	5	No	Yes	Levodopa
20	79/F	14	Yes	Yes	Levodopa
21	75/F	7	Yes	Yes	Levodopa, pramipexole, amantadine
22	48/M	2	No	Yes	Levodopa

Clinical data and current medical treatment of all patients included in the study.
Ach, anticholinergics; F, female; M, male.

and after treatment. All statistical analyses were done with Statistical Package for the Social Sciences software, version 19.

RESULTS

Patient Characteristics

The study group consisted of 13 men and 9 women with a mean (SD) age of 65 (10.2) years. The clinical characteristics and regular medications of the patients are described in Table 1. Mean (SD) disease duration was 7.3 (4.8) years. The median score on the Hoehn and Yahr scale was 1.5 (range, 1 to 3). Seven patients (3 men, 4 women) had motor fluctuations. The patients who had fluctuations were younger and had a shorter disease duration than those who did not, but the differences were not significant (mean [SD] age, 63.7 [12.7] years vs 65.6 [9.4] years; mean [SD] disease duration, 7.7 [4] years vs 7 [5.2] years). Three were assessed during the off period; 4, during the on period.

Effect of Cannabis on Motor Symptoms

Analysis of the interrater variability yielded a high concordance in motor scores between the 2 examining physicians both before treatment (Pearson correlation, 8.4) and after (Pearson correlation, 8.8). Therefore, for convenience, we present only the results of one of the raters (L.I.).

The mean (SD) total motor UPDRS score improved significantly from 33.1 (13.8) at baseline to 23.2 (10.5) after cannabis consumption ($t = 5.9$, $P < 0.001$). The change in motor UPDRS score was significant in both patients with and without response fluctuations (Fig. 1). Among the patients with response fluctuations, the off UPDRS score improved by 55% in 2 patients, with no change in 1 patient; the on UPDRS score improved by 50% in 2 patients, with no change in 2. Analysis by specific motor symptoms revealed a significant improvement in tremor, rigidity, and bradykinesia after cannabis consumption. There was no effect on posture (Table 2).

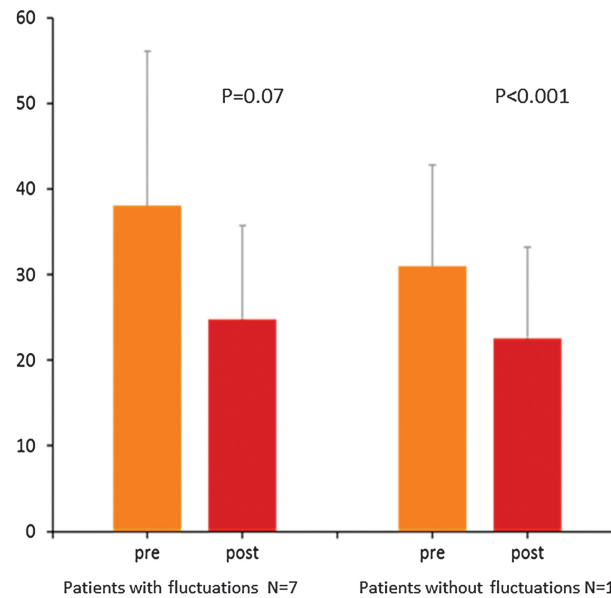

FIGURE 1. The effect of cannabis on the motor UPDRS score in the patients with and without response fluctuations.

TABLE 2. Effect of Cannabis on Motor UPDRS Score

	UPDRS		
	Before Smoking Cannabis	**After Smoking Cannabis**	***P***
Tremor (items 20–21)	7.55 (4.79)	3.64 (2.8)	0.000
Rigidity (item 22)	7.55 (3.79)	6.48 (3.56)	0.004
Bradykinesia (items 23–27, 30–31)	13.12 (6.88)	8.62 (5.5)	0.000
Posture (items 28–29)	1.90 (1.58)	1.55 (1.1)	0.056

The effect of Cannabis on different categories of the UPDRS.

Effect of Cannabis on Non–Motor Symptoms

The visual analog scale score decreased significantly, from 5.4 (3.7) at baseline to 1.7 (2.6), after cannabis smoking ($t = 5.3$; $P < 0.001$). Corresponding scores on the present pain intensity scale were 2.7 (1.7) and 0.8 (1.1) ($t = 5.9$, $P < 0.001$). Twelve patients reported greatly improved quality of sleep during cannabis treatment, and 8 had mild relief.

No significant adverse effects were observed during the study. One patient had hypoglycemia that resolved after oral glucose intake, and 1 patient complained of dizziness. The main adverse effects of long-term smoking reported by the patients were somnolence, drowsiness, palpitations, and bad taste.

DISCUSSION

The use of the *C. sativa* plant as a medicinal preparation dates back to ancient Asian pharmacopeia. Among its well-documented medical benefits are amelioration of nausea and vomiting, stimulation of hunger in patients receiving chemotherapy or with AIDS, lowered intraocular eye pressure, as well as general analgesic effects.[2–6] Research on the neuroprotective and therapeutic effects of cannabis in neurodegenerative diseases was spurred by the discovery of the endogenous cannabinoid system.[8] The cannabinoid signaling system in the brain interacts with G-protein–coupled cannabinoid receptors. Endocannabinoids, synthesized on demand, activate the cannabinoid receptors, thereby depressing the release of neurotransmitters, mainly glutamate. Tetrahydrocannabinol, the main psychoactive component of cannabis, exerts its most prominent effects via its actions on 2 types of cannabinoid receptors: the CB1 receptor, found primarily in the brain as well as in some peripheral tissues, and the CB2 receptor, found primarily in peripheral tissues but also expressed in neuroglial cells.[9,10]

Studies of the potential therapeutic effect of cannabinoids on PD have produced conflicting results. Among those conducted in the MPTP and 6-OHDA primate models, some found that cannabinoid improved motor activity,[11–13] whereas others reported that it did not.[14,15] Given that the mechanism of action of cannabinoids is mediated by glutamate, several clinical trials focused on the effect of cannabis on dyskinesias in PD. Again, the results were inconclusive. One randomized, double-blind, placebo-controlled crossover trial in 7 patients found a significant reduction in dyskinesias in response to treatment with the cannabinoid receptor agonist, nabilone.[16] However, a larger double-blind crossover study in 19 patients yielded no beneficial effect with Cannador (an extract of *C. sativa* containing Δ9-THC and cannabidiol) on either dyskinesias or UPDRS scores.[17] An observational study of 5 patients found no effect on tremor,[18] but an anonymous questionnaire survey reported that bradykinesia seemed to be the symptom most commonly improved by cannabinoids, followed by muscle rigidity and tremor.[19]

The present study suggests that smoking cannabis has a beneficial effect on tremor and rigidity, a lesser effect on bradykinesia, and only a trend for improvement of posture. The findings were consistent in patients with and without response fluctuations. In patients with fluctuations, both the off and on motor UPDRS scores improved. One patient with young-onset PD examined in the off period responded dramatically to inhaled cannabis, to the extent of a clear "on" gained by levodopa. Cannabis also had a positive impact on non–motor symptoms. Scores on pain scales dropped significantly, and the patients reported better quality of sleep. The latter finding might be attributable partly to nocturnal pain relief and partly to the tranquilizing and somnolent effect of the drug. The psychotropic effects of cannabis and the perception of well-being often associated with its use may also be responsible for the favorable response here and in other studies. Although cannabinoids have high lipid solubility and THC is still detected weeks after drug intake,[20] most of our patients reported that the benefits of a single dose were short-lasting (2–3 hours). During the study, cannabis was generally well tolerated.

The open-label design of this study has inherent limitations of a placebo effect and rater bias. We tried to overcome the latter problem by using 2 raters, and the low interrater variability partly ensures the reliability of the results. Nevertheless, bias and placebo effect can explain the discrepancy between the favorable results of the present study and the negative results of other clinical, double-blind studies. In the setting of the present study, it was difficult to perform a placebo-controlled trial because of the conspicuous and characteristic smell of the cannabis cigarette. Another drawback of the study is that the patients were assessed at 1time point only. Longer assessment of the clinical response is warranted to clearly establish a beneficial effect of cannabis on the motor symptoms of PD.

In conclusion, this observational study is the first to report an amelioration of both motor and non–motor symptoms in patients with PD treated with cannabis (medical marijuana). The study opens new venues for treatment strategies in PD especially in patients refractory to current medications. It may promote legalization of cannabis in other countries and should encourage pharmaceutical companies to conduct controlled studies with a more purified substance. Although promising, our results should be interpreted with caution and confirmed in larger double-blind, placebo-controlled studies conducted over a longer term, with special attention to the possible addictive potential of the drug.

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